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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, RUIXIANG	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/31/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,347	BENOWITZ, LARRY I.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *3,7,32-34 and 38-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8-31,35-36, and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicants' election with traverse of Group I, Claim 1 (in part), 2, 4-28, 29 (in part), 30, 31, 35 (in part), 36 (in part), 37, 38, and 44-46, drawn to a method comprising administering to a subject with spinal cord injury a therapeutically effective amount of a macrophage-derived factor, oncomdulin, in Paper No. 9 filed on 10/15/2002 is acknowledged. Applicants' election with traverse of species non-hydrolyzable cAMP analogs and inosine is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. Claims 1-46 are pending. Claims are 1, 2, 4-6, 8-31, 35-37, and 44-46 under consideration.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to a provisional application, 60/208,778 filed on June 1, 2000.

Claim Rejections—35 USC § 112, 1st paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 6, 8-14, 18-28, 35, and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of comprising administering to a subject therapeutically effective amount of oncomodulin by introduction into a region of neuronal injury of retinal ganglion cells and producing an effect on neuronal survival, regeneration, and axonal outgrowth, does not reasonably provide enablement for a method of comprising administering any macrophage-derived factors, or producing any effects (other than neuronal survival, regeneration, and axonal outgrowth) on any neurons (other than retinal ganglion cells). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The factors considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1, 2, 6, 8-14, 18-28, 35, and 37 are drawn to methods comprising administering to a subject therapeutically effective amount of a macrophage-derived factor (such as the elected oncomodulin) with or without an axogenic factor (such as inosine) and producing a neurosalutary effect in said subject. There are two key issues which are related to the scope enablement.

First, activated monocytes release a host of cytokines and growth factors that can stimulate neurons directly or indirectly via glial stimulation, as acknowledged in the instant disclosure (4th paragraph of). However, the instant disclosure only discloses oncomodulin (and unelected TGF-β) stimulated retinal ganglion cells to regenerate their axons *when tested in culture* (lines 23-30 of page 25). There is no sufficient information indicating whether other macrophage-derived factors would have the same effects as that of oncomodulin.

Second, according to the definition given in the disclosure (3rd paragraph of page 3), a neurosalutary effect means a response or result favorable to the health of function of a neuron, of a part of the nervous system, or of the nervous system generally. Thus, it encompasses neuroprotective effects or even treatment of neurological disorders. However, the disclosure merely discloses the effect of Zymosan, a yeast cell wall preparation which comprises oncomodulin, on retinal ganglion cells by introduction the Zymosan into a region of injured optic nerve: neuronal survival, regeneration, and axonal outgrowth. The instant disclosure fails to show that injection of oncomodulin directly caused such neuronal protection effects. What is shown here in the instant case is that oncomodulin and TGF-β) stimulated retinal ganglion cells to regenerate their axons *when tested in culture*.

In view of the complexity of the nature of neurological diseases, it is highly unpredictable whether a factor that promotes neuronal survival in vitro would work in vivo or whether a factor that works on one type of neuron would work on another type of neuron. For example, TGF-β promotes survival of rat spinal cord motorneurons and dopaminergic neurons, but it fails to prevent neuronal degeneration in a rat

model (*IDS*, Flanders et al, Prog. Neurobiolo. 54:71-85, 1998; see e.g., Abstract). In addition, the instant disclosure fails to provide working examples, sufficient guidance, or information on how to practice the claimed broad methods. Therefore, it would require undue experimentation for one skilled in the art to use the claimed invention commensurate in scope with the claims.

6. Claims 4, 5, 15-17, 29-31, 36, and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claims 4, 5, and 36 are drawn to methods comprising administering to a subject a cAMP modulator, which encompasses virtually anything that has an effect on cAMP including non-hydrolyzable cAMP analogues. The disclosure only demonstrates the effect of a single modulator, TGF-β, synergized with AF-1 and elevated cAMP. However, there is no guidance provided teaching how to extrapolate this single example to predict which of the many potential modulators of cAMP would be reasonably expected to have a similar effect in this system. There are also no working examples indicating that any cAMP modulators, including the elected species, non-hydrolyzable cAMP analogues would stimulate retinal ganglion cells to regenerate their axons when used with with oncomodulin. In fact, a nonohydrolyzed analogue of cAMP, sp-8-Br-cAMPs, was shown to be inactive in inducing axon outgrowth by Iorio et al. (IDS, Drug Development Research 52:303-315, 2001; see especially Fig. 1).

Claims 15-17 are drawn to methods comprising different routes of administration of a macrophage-derived factor to a subject. The instant disclosure is limited to a single intraocular injection around optic nerve via a posterior approach (page 15). There is no sufficient guidance or working example demonstrating that administering by any recited routes of administration of a macrophage-derived factor to a subject would produce an effect on neuronal survival, regeneration, or axonal outgrowth. It has been shown that the ability of TGF-β to protect neurons in vivo from degeneration may depend on the route of administration of TGF-β, as well as the type of injury, the location and the type of neurons (IDS, Flanders et al, Prog. Neurobiolo. 54:71-85, 1998; especially 4th paragraph of left column of page 82).

Claims 29-31, and 44-46 are drawn to methods of treating neurological disorders, such a spinal cord injury. While the instant disclosure discloses that when tested in culture, oncomodulin stimulated retinal ganglion cells to regenerate their axons (lines 27-28 of page 25). There is no any disclosure on how the claimed methods comprising administering a macrophage-derived factor, such as oncomodulin, would be used for treating neurological disorders. Due to complexity of the nature of neurological disorders, it is unpredictable whether a specific neurological disorder, such a spinal cord injury, can be successfully treated by a factor, which has a neuroprotective effect in vitro (IDS, Flanders et al, Prog. Neurobiolo. 54:71-85, 1998; see e.g., bottom of left column of page 81). This is because most in vitro studies examine the effect of an agent on a single cell type, while in vivo there are complex interactions between multiple cell types. In addition, since the effects of many cytokines are context-dependent, other cytokines and

extracellular matrix proteins can modulate the biological actions of the agent of interest.

Accordingly, the disclosure fails to enable the claimed various methods. It would require undue experimentation for one skilled in the art to use the claimed invention embraced by the instant claims.

Claim Rejections—35 USC § 112, 1st paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 4-6, 8-31, 35, and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 1, 4-6, 8-31, 35, and 36 are drawn to methods comprising administering to a subject a therapeutically effective amount of a macrophage-derived factor, thereby producing a neurosalutary effect in said subject. Thus, the claims recite a genus of macrophage-derived factors.

However, the specification merely discloses two macrophage-derived factors, oncomodulin and TGF-β, which stimulated retinal ganglion cells to regenerate their axons *when tested in culture* (lines 23-30 of page 25) and a method of use. The two disclosed molecules, oncomodulin and TGF-β, are structurally unrelated molecules. The instant disclosure fails to provide the critical structural features to adequately

describe a genus of factors that may be used successfully in such a method. There is no sufficient information provided in the instant disclosure sufficient for one skilled in the art to identify whether other macrophage-derived factors would have the same effects as that of oncomodulin or TGF-β.

Therefore, due to the breadth of the claimed genus and lack of the definitive structural of the claimed genus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the claimed genus.

Claim Rejections—35 USC § 112, 2nd paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 2, 4-6, 8-31, and 35-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 35, and 36 are indefinite because each claim recites "a macrophage-derived factor". It is unclear what is included or excluded in the term. Claims 4-6, 8-31 depend upon claim 1.

Claim 1 and 35-37 are indefinite because each claim recites "a neurosalutary effect". It is unclear what the metes and bounds of this term are. Claims 2, 4-6, 8, 14-31 depend upon claim 1.

Claim Rejections—35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 9-12, 14, 18, 27, and 30, are rejected under 35 U.S.C. 102(b) as being anticipated by Flanders et al. (IDS, Transforming growth factor-betas in neurodegenerative disease. Prog. Neurobiolo. 54:71-85, 1998).

Flanders et al. teach that TGF-β, a macrophage-derived factor, has been demonstrated to protect neurons from degeneration in one animal model. Destruction of the adrenal medulla leads to disappearance of the sympathetic preganglionic spinal cord neurons. Implantation of gelfoam soaked with TGF-β2 into the adrenal medulla wound cavity rescues all spinal cord neurons. Since "a neurosalutary effect" reads on protection of neurons from degeneration when interpreted as broadly as possible, the reference of Flanders et al. meets the limitations of the generic method of claim 1.

Claim Objections

13. Claims 35-37 are objected to because of the following informalities: claim 35 is essentially the same as claim 6, claim 36 is essentially the same as claim 4, whereas claim37 is essentially the same as claim 2. Appropriate correction is required.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ruixiang Li
Examiner
December 12, 2002

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